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Correlation between inflammatory parameters and bloodstream infections caused by multidrug resistant Gram-negative bacteria in critically ill COVID-19 patients – retrospective single-center study

Povezanost upalnih parametara i infekcija krvi uzrokovanih multirezistentnim Gram negativnim bakterijama kod COVID-19 pozitivnih bolesnika liječenih u jedinici intenzivnog liječenja – retrospektivna studija jednog centra

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Descriptors
COVID-19 PANDEMICS;
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KLEBSIELLA

SUMMARY. *Objectives:* During the COVID-19 pandemics we have seen in critically ill COVID-19 patients treated in the intensive care unit the parallel outbreak of multidrug resistant Gram-negative bacteria bloodstream infections, mainly Acinetobacter baumannii and Klebsiella pneumoniae. *Methods:* We conducted a retrospective cohort single-center study. The aim was to investigate the incidence, etiology and impact of intensive care unit bloodstream infections in COVID-19 patients admitted to the COVID-19 intensive care unit with a known burden of multidrug resistance and to evaluate the possibility that inflammatory parameters levels measured at two different time points of treatment can early predict multidrug resistant Gram-negative bacteria bloodstream infections and enable timely beginning of bacterial targeted antimicrobial therapy. *Results:* Our study confirmed that procalcitonin values of 2,46 mcg/L and neutrophil/lymphocyte ratio of 28,9 could be a reliable indicators for high risk stratification of multidrug resistant Gram-negative bacterial infection origin in critically ill COVID-19 patients (Mann Whitney U test, P=0,02). *Conclusion:* Monitoring dynamic shift of inflammatory parameters in critically ill COVID-19 patients could reliably help clinician to recognize the multidrug resistant Gram-negative bacteria bloodstream infections and start with the antimicrobial therapy in a timely manner.

Deskriptori
COVID-19;
GRAM NEGATIVNE BAKTERIJE;
ACINETOBACTER BAUMANNII;
KLEBSIELLA

SAŽETAK. *Cilj istraživanja:* Tijekom COVID-19 pandemije uočili smo kod kritično bolesnih COVID-19 pozitivnih bolesnika liječenih na odjelu intenzivne njege paralelno izbijanje infekcija krvi uzrokovanih multirezistentnim Gram negativnim bakterijama, uglavnom Acinetobacter baumannii i Klebsiella pneumoniae. U praksi rezultati mikrobiološke potvrde infekcija krvi završeni su s određenom vremenskom odgodom. Stoga primarni cilj istraživanja bio je odrediti povezanost upalnih parametara (leukociti, limfociti, neutrofili, omjer neutrofila i limfocita, C-reaktivni protein, prokalcitonin) mjerenih u dvije različite vremenske točke (dan prijema u jedinicu intenzivnog liječenja i dan nastanka infekcija krvi potvrđenih pozitivnim hemokulturama) i nastanka infekcija krvi uzrokovanih multirezistentnim Gram negativnim. Sekundarni ciljevi istraživanja bili su istražiti učestalost, etiologiju i utjecaj infekcija krvi uzrokovanih multirezistentnim Gram negativnim bakterijama na ishod liječenja COVID-19 pozitivnih bolesnika. *Materijali i metode:* Proveli smo retrospektivno kohortno istraživanje u Kliničkoj bolnici Dubrava na intenzivističkom odjelu COVID-19 pozitivnih bolesnika u vremenskom period od 31. listopada 2020. godine do 31. ožujka 2021. godine. U istraživanju je sudjelovalo 166 COVID-19 pozitivnih bolesnika koji su zadovoljili kriterije uključenja u istraživanje. 122 COVID-19 bolesnika imali su mikrobiološki potvrđenu infekciju krvi uzrokovanu multirezistentnim Gram negativnim bakterijama. Kontrolna gupa imala je 44 COVID-19 bolesnika koji nisu razvili infekciju krvi. Svi podaci bolesnika skupljali su se iz povijesti bolesti i elektroničke baze podataka. *Rezultati:* Naša studija potvrdila je cut-off vrijednosti upalnih parametara prokalcitonina od 2,46 mcg/L i omjer neutrofila/limfocita od 28,9 kao pouzdane pokazatelje stratifikacije visoko rizičnih COVID-19 bolesnika za nastanak infekcije krvi uzrokovane multirezistentnim Gram negativnim bakterijama, Acinetobacter baumannii i Klebsiella pneumoniae (Mann Whitney U test, P=0,02). *Zaključak:* Dinamički monitoring upalnih parametara sa cut-off vrijednostima proklacitonina i omjera neutrofila i limfocita u različitim vremenskim intervalima u kritično bolesnih COVID-19

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pozitivnih bolesnika pouzdani je pokazatelj visokog rizika nastanka infekcija krvi uzrokovanih multirezistentnim Gram negativnim bakterijama koji u kliničkoj praksi omogućuje pravovremeno uvođenje ciljane antimikrobne terapije prije dospijeća mikrobiološke potvrde.

Bloodstream infections (BSIs) have high morbidity and mortality[1]. As we have witnessed during the COVID-19 pandemics the outbreak of BSIs caused by multidrug resistant Gram-negative bacteria (MDRGN bacteria) mainly Acinetobacter baumannii and Klebsiella pneumoniae in the critically ill COVID-19 patients made the treatment more difficult and unsuccessful with bad outcomes for many of these COVID-19 patients[1]. Patel et al. demonstrated a rapid outbreak of MDRGN bacteria in COVID-19 patients due to many important and modifiable risk factors such as prolonged critical illness, high antibiotic and corticosteroid use, modified infection prevention control and high occupancy of intensive care unit (ICU)[2]. Also, Garcia et al. revealed that prolonged ICU hospitalization, antibiotic exposure and invasive device implementation such as vascular catheters and endotracheal tubes are associated with a higher risk of MDRGN bacteria colonization and finally bloodstream infections origin in COVID-19 patients[3]. Since the MDRGN bacteria BSIs are dynamic illness, the timely and correct diagnosis followed by antimicrobial therapy administration is crucial for higher chance of patients survival[4,5]. Another problem is systemic inflammatory syndrom in critically ill COVID-19 patients which usually manifests with symptoms as fever, tachycardia, hyperventilation, leukocytosis, and increased inflammatory parameters such as procalcitonin (PCT) and C-reactive protein (CRP), and sometimes can conceal the signs of BSIs. Although the blood culture is the golden standard for BSIs diagnosis, many times due to deteriorated patients clinical status and delayed blood culture results it is necessary to start with the adequate antimicrobial therapy as early as possible[4,6]. Thereby, we conducted a retrospective study to investigate if the inflammatory parameters such as leukocytes, neutrophils, lymphocytes, neutrophil/lymphocyte ratio (NLR), CRP and PCT measured in two different time points (on the day of admission in the COVID-19 ICU and on the day of BSIs diagnosis confirmed by positive blood cultures) correlate with the appearance of MDRGN bacteria BSIs in critically ill COVID-19 patients and whether they could be an early and helpful biomarkers for the early MDRGN bacteria BSIs diagnosis.

Materials and methods

We conducted a retrospective cohort single-center study at the Clinical Hospital Dubrava at the Department of COVID-19 ICU. All patients data required to analyse the inflammatory parameters in the COVID-19 patients were collected from the medical records and the University Hospital Dubrava electronic medical database. The study included all patients with COVID-19 infection, confirmed by reverse transcription polymerase chain reaction on nasopharyngeal swabs, consequtively admitted to the COVID-19 ICU at the University Hospital Dubrava between the October 31, 2020, and March, 31, 2021. Other inclusion criteria were male and female gender aged more than 18 years, BSIs caused by MDRGN bacteria Acinetobacter baumannii and Klebsiella pneumoniae 48 hours after the admission in the COVID-19 ICU. ICU BSIs were defined as a pathogen isolation from >=1 blood specimen obtained at more than 48 hours after ICU admission. In the patients with >=2 BSIs, only the first one was included. Exclusion criteria were inadequate medical database and not accomplished inclusion criteria, patients with malignant disease, immune system disorders such as systemic lupus erythematosus or rheumatoid arthritis, and BSIs caused by Gram-positive bacteria. Baseline clinical and epidemiological data together with illness severity assessed by APACHE II,SOFA and SAPS II score were recorded (table 1). We investigated the incidence, etiology and impact of ICU BSIs in COVID-19 patients admitted to the COVID-19 ICU with a known burden of multidrug resistance (table 1)[5]. We focused on BSIs because these represent definite infection events, while distinction between colonization and infection is more difficult with other specimen types[7]. Blood samples were collected for simultaneous detection of blood culture and inflammatory parameters. Study goal was to evaluate the possibility that inflammatory parameters levels can early predict MDRGN bacteria BSIs and enable timely beginning of bacterial targeted antimicrobial therapy. Limitation of the study was that it was conducted retrospectively. Also it is difficult to compare it with other studies due wide variations in the local epidemiological picture and definitions of resistance.

Statistical analysis

Categorical data are presented by absolute and relative frequencies. Differences of categorical variables were tested by Chi-square test. Normality of distribution for continuous variables was tested by using Shapiro-Wilk test. Since the distribution was not normal, nonparametric tests were used and continuous data were presented with median and limits of interquartile range. Differences in continuous variables between the independent groups were tested by Mann Whitney U test, with 95% confidence interval (CI). Differences

Table 1. Baseline characteristics of critically ill COVID-19 patients with multidrug resistant Gram-negative bloodstream infections casued by Acinetobacter baumannii and Klebsiella pneumoniae. P value <0,05 was considered significant. Osnovne karakteristike COVID-19 pozitivnih bolesnika.

	The treatment outcome of MDRGN BSIs patients			Difference‡ 95% CI	P value
	Positive (n=16)	Negative (n=106)	Total (n=122)		
Patient's characteristics					
Age (years) [Median (IQR)]	59 (54 – 73)	72 (64 – 79)		9 (4 to 16)	**0,003**†
Gender [n (%)]					
Female	5 (31)	21 (20)	26 (21,3)		0,33*
Male	11 (69)	85 (80)	96 (78,7)		
Comorbidity [n (%)]					
Coronary artery disease	1 (6)	21 (20)	22 (18)		0,30*
Cardiomyopathy	4 (25)	9 (8)	13 (10,7)		0,07*
Chronic obstructive pulmonary disease	1 (6)	8 (8)	9 (7,4)		> 0,99*
Chronic renal insufficiency	0	10 (9)	10 (8,2)		0,36*
Diabetes mellitus	5 (31)	39 (37)	44 (36,1)		0,67*
Neurologic disease	2 (13)	15 (14)	17 (13,9)		> 0,99*
ICU admission					
APACHE II score [Median (IQR)]	13 (8 – 16)	13 (10 – 16)	13 (10 – 16)	1 (–2 to 4)	0,50†
SOFA score [Median (IQR)]	3 (2 – 4)	4 (2 – 5)	4 (2 – 5)	0 (0 to 1)	0,19†
SAPS II score [Median (IQR)]	25 (21 – 31)	32 (24 – 38)	30 (23 – 37)	6 (1 to 11)	**0,02**
COVID19 characteristics at ICU admission					
Day of disease [Median (IQR)]	9 (8 – 10)	8 (6 – 14)	9 (6 – 13)	0 (–2 to 3)	0,93†
Aysmptomatic [n (%)]	0	0	0		–
Unilateral pneumonia [n (%)]	1 (6)	2 (2)	3 (2,5)		0,35*
Bilateral pneumonia [n (%)]	14 (88)	104 (98)	118 (96,7)		0,08*
PaO_2/FiO_2 [Median (IQR)]	62 (50,6 – 171,8)	70 (52,1 – 92,9)	70 (52 – 94)	–5 (–51 to 11,1)	0,49†
High flow oxygen therapy(days) [Median (IQR)]	6 (2 – 13)	2 (1 – 5)	2 (1 – 9)	–3 (–6 to 1)	**0,005**†
Invasive ventilation (days) [Median (IQR)]	12 (5 – 27)	10 (7 – 14)	10 (7 – 14)	–2 (–9 to 3)	0,44†
Total length of treatment [Median (IQR)]	28 (17 – 39)	14 (10 – 20)	15 (10 – 21)	–11 (–20 to –6)	**<0,001**†
Immunomodulatory therapy					
Corticosteroids [n (%)]	10 (63)	68 (64)	78 (63,9)		0,89*
Dosage, [n (%)]					
Low (1–8 mg)	5 (56)	31 (46)	36 (47)		> 0,99*
Medium (9–16 mg)	2 (22)	18 (26)	20 (26)		
High (>16 mg)	2 (22)	19 (28)	21 (27)		
MDRGN bacteria bloodstream infections (BSIs)					
Time between ICU admission and BSIs (days) [Median (IQR)]	13 (10 – 15)	8 (5 – 10)	8 (6 – 12)	–5 (–7 to –2)	**<0,001**†
Day of the COVID19 disease when BSIs was diagnosed[Median (IQR)]	21 (17 – 25)	17 (11 – 22)	20 (12 – 23)	–4 (–8 to 0)	0,06†
Antimicrobial treatment before BSIs [n (%)]	16 (100)	97 (92)	113 (93)		0,60*
Length of ICU stay (days) [Median (IQR)]	22 (16 – 33)	12 (8 – 17)	13 (9 – 19)	–10 (–15 to –5)	**<0,001**†
Length of hospital stay (days) [Median (IQR)]	34 (26 – 42)	15 (11 – 21)	17 (11 – 22)	–19 (–23 to –12)	**<0,001**†

*Chi-square Test; †Mann Whitney U test; ‡Hodges-Lehmann Median Difference. Bold denotes statistical significance.

in values of continuous dependent variables were tested by Wilcoxon test. Level of significance was set to Alpha = 0,05. Statistical analysis was performed with MedCalc® Statistical Software version 19.6 and SPSS (IBM Corp. Released 2013. IBM SPSS, Ver. 21.0. Armonk, NY).

Table 2. Difference in inflammatory parameters in COVID-19 patients admitted to the Intensive care unit who developed multidrug resistan Gram-negative bloodstream infections mesaured at two different time points: on the day of admission to the intensive care unit and on the day when bloodstream infections were confirmed with positive blood cultures. P value <0,05 was considered significant.

Tablica 2. Razlika u vrijednostima upalnih parametara u COVID-19 pozitivnih bolesnika primljenih u Jedinicu intenzivnog liječenja izmjerenih u dvije vremenske točke: dan prijema u Jedinicu intenzivnog liječenja i dan kada je mikrobiološki potvrđena infekcija multirezistentnim Gram negativnim bakterijama.

	Median (Interquartil range)		Difference‡	95% CI	P* value
	Admission day ICU (n = 122)	MDRGN bacteria BSIs Group (n = 122)			
Leukocytes (10^9/L)	10,9 (8,63 – 16,08)	14 (9,3 – 18)	2,1	0,95 to 3,2	**<0,001**
Lymphocytes (%)	5,8 (2,73 – 7,73)	3,2 (2,1 – 5,7)	–1,6	–2,4 to –0,8	**<0,001**
Neutrophils (%)	88,9 (85,2 – 92,6)	92,5 (88,8 – 94,6)	2,7	1,4 to 3,9	**<0,001**
Neutrophil/lymphocyte ratio (NLR)	15,4 (10,7 – 34,2)	28,9 (16,0 – 44,0)	8,22	2,9 to 12,6	**<0,001**
Thrombocytes (10^9/L)	242 (168,5 – 314,5)	211 (144,3 – 295)	–29	–50 to –7	**0,01**
Procaltinon (mcg/L)	0,99 (0,29 – 3,83)	2,46 (1,05 – 8,69)	0,97	0,17 to 3,02	**0,01**
C-reactive protein (mg/L)	164,2(117,1 – 234,2)	167,9 (96,6 – 240,8)	0,6	–20,1 to 20,9	0,95

*Wilcoxon Test; ‡Hodges-Lehmann Median Difference. Abbreviations: CI – confidence interval. Bold denotes statistical significance

Table 3. Difference in inflammatory parameters in COVID-19 patients on the day of admission to the Intensive care unit between the control COVID-19 patients who did not develop bacterial infections and the COVID-19 patients who developed the multidrug resistant Gram-negative bloodstream infections.P value <0,05 was considered significant.

Tablica 3. Razlika u vrijednostima upalnih parametara na dan prijema u Jedinicu intenzivnog liječenja između COVID-19 pozitivnih bolesnika koji su razvili infekciju krvi multirezistentnim Gram negativnim bakterijama i kontrolne grupe.

	Median (Interquartil range)		Difference‡	95% CI	P* value
	Control Group (n = 48)	MDRGN bacteria BSIs Group (n = 122)			
Leukocytes (10^9/L)	10,5 (8,3 – 16,3)	10,9 (8,63 – 16,08)	0	–1,6 to 1,6	0,99
Lymphocytes (%)	5,4 (3,7 – 9,2)	5,8 (2,73 – 7,73)	–0,3	–1,6 to 0,9	0,61
Neutrophils (%)	90,1 (85,9 – 92,9)	88,9 (85,2 – 92,6)	–0,4	–2,1 to 1,3	0,67
Neutrophil/lymphocyte ratio (NLR)	16,7 (9,9 – 24,3)	15,4 (10,7 – 34,2)	0,75	–3,04 to 4,72	0,69
Procalcitonin (mcg/L)	0,29 (0,13 – 2,59)	0,99 (0,29 – 3,83)	0,29	0,04 to 0,72	**0,02**

* Mann Whitney U test; ‡Hodges-Lehmann Median Difference. Abbreviations: CI – confidence interval. Bold denotes statistical significance

Results

The study included 166 COVID-19 cases admitted to the COVID-19 ICU (table 1). The MDRGN bacteria BSIs group consisted of 122 (73,5%) COVID-19 cases with confirmed BSIs caused by MDRGN bacteria, and the control group consisted of 44 (26,5%) COVID-19 cases who had sterile bacterial specimen during COVID-19 ICU stay (table 1). Bloodstream infections caused by multidrug resistant Acinetobacter baumannii was isolated in 102 (84%) MDRGN bacteria BSIs cases, and BSIs caused by multidrug resistant Klebsiella pneumoniae was isolated in 20 (16%) MDRGN bacteria BSIs cases (table 1).The MDRGN bacteria BSIs cases median age with interquartile range (IQR) was 71 (62–78) years (table 1). In total 106 (87%) of MDRGN bacteria BSIs cases died in the COVID-19 ICU or hospital. The MDRGN bacteria BSIs cases who died were significantly older, age median 72 years versus 59 years in the MDRGN bacteria BSIs cases who survived (Mann Whitney U test,p=0,003) (table 1). Considering the gender, MDRGN BSIs were prevalent in the male gender 96 (78,7%) versus female gender 26 (21,3%) (table 1). MDRGN bacteria BSIs were more common in those cases with history of diabetes mellitus, 44 (36,1%) cases (table 1). There was no significant difference in the APACHE II and SOFA score according to outcome, while SAPS II score was significantly higher in MDRGN bacteria BSIs cases with negative outcome (median 32, IQR 24–48, Mann-Whitney U test, P=0,02) (table 1). Median length of the COVID-19 ICU stay was 9 days (IQR 6–13) days (table 1). 118 (96,7%) of MDRGN bacteria BSIs cases had bilateral COVID-19 pneumonia (table 1). Length of treatment with high flow oxygen therapy in MDRGN bacteria BSIs cases with negative outcome was statistically significant shorter (Mann Whitney U test, P=0,005) versus cases with positive outcome (table 1).The length of the COVID-19 ICU stay and the length of hospital stay in MDRGN bacteria BSIs cases with negative outcome was also significantly shorter in comparison to cases

Table 4. Correlation of inflammatory parameters and development of multidrug resistant Gram-negative bloodstream infections in critically ill COVID-19 patients. We used bivariate logistic regression. P value <0,05 was considered significant.

Tablica 4. Korelacija između upalnih parametara i nastanka infekcije krvi uzrokovane multirezistentnim Gram negativnim bakterijama u COVID-19 kritičnih bolesnika.

	ß	Wald	P value	OR	95% CI
Leukocytes (10^9/L)	–0,01	0,10	0,75	0,99	0,95 to 1,04
Lymphocytes (%)	–0,02	0,23	0,63	0,98	0,91 to 1,06
Neutrophils (%)	–0,01	0,09	0,77	0,99	0,95 to 1,04
Neutrophil/lymphocyte ratio (NLR)	0,01	1,57	0,21	1,01	0,99 to 1,03
Procalcitonin (mcg/L)	0,004	0,56	0,46	1,00	0,99 to 1,02

β – Regression coefficient. Abbreviations: OR – odds ratio; CI – confidence interval.

with positive outcome(Mann Whitney U test, P<0,001) (table 1). The study revealed that application of immunomodulatory corticosteroid therapy in low (1–8 mg), medium (9–16 mg), and high (>16 mg) doses did not correlate with the outcome (table 1). MDRGN bacteria BSIs cases with negative outcome were diagnosed with MDRGN bacteria BSIs earlier during COVID-19 disease in comparison to cases with positive outcome (medijan 17 vs 21 days, p=0,06) (table 1). Also, MDRGN bacteria BSIs cases with negative outcome developed MDRGN bacteria BSIs earlier during their stay in the COVID-19 ICU in comparison to those with positive outcome (8 vs 13 days, Mann Whitney U test, P<0,001) (table 1). As well length of stay in the COVID-19 ICU and hospital was statistically shorter for the MDRGN bacteria BSIs cases with negative outcome in comparison to cases with positive outcome (Mann Whitney U test, P < 0,001) (table 1). Inflammatory parameters leukocytes, neutrophils, NLR, PCT and CRP were significantly elevated at the day of MDRGN bacteria BSIs confirmation with positive blood culture in comparison to inflammatory parameters measured on the day of admission to the COVID-19 ICU (table 2). Moreover, inflammatory parameters lymphocytes and thrombocytes were significantly lower at the day of MDRGN bacteria BSIs versus the value of these parameters measured on the day of admission to the COVID-19 ICU (table 2). There was no statistical difference in values of inflammatory parameters between MDRGN bacteria BSIs cases and control cases on the day of admission to the COVID-19 ICU except in the PCT value (table 3). Hence, PCT values in the MDRGN bacteria BSIs cases on the day of admission were significantly higher in comparison to control cases (median 0,99 mcg/L vs 0,29 mcg/L, Mann Whitney U test, P=0,02) (table 3). However, using bivariant logistic regression we did not find that any of the studied inflammatory parameters could be predicitive for MDRGN bacteria BSIs development in the COVID-19 critically ill patients (table 4).

Discussion

According to the studies, main risk factors connected with MDRGN bacteria BSIs are male gender, patients older than 60 years, and previous use of antimicrobial therapy especially cephalosporins, carbapenems and fluoroquinolons[1]. During the COVID-19 pandemics we wittnessed the outbreak of ICU BSIs caused by MDRGN bacteria Acinetobacter baumannii and Klebsiella pneumoniae. In our hospital the incidence of MDRGN bacteria BSIs was notably higher in comparison to earlier non-COVID-19 period (25/1000 ICU days versus 4/1000 ICU days). Similary, our study results also showed the prevalence of MDRGN bacteria BSIs in male gender, older patients and those with history of diabetes mellitus. Also patients with these risk factors had greater chance for the negative outcome, especially if they were older. As well, many of the patients admitted to the COVID-19 ICU before MDRGN bacteria BSIs event had previous antimicrobial therapy exposure. The most common prescribed antimicrobial therapy was ceftriaxone, followed by meropenem and piperacilin/tazobactam. Previous empiric unnececssary antimicrobial therapy could also be a risk factor for development of MDRGN bacteria BSIs. In our study we did not confirm correlation of immunomodulatory corticosteroid therapy applied in different dosages (low,medium,high) with the outcome of the MDRGN bacteria BSIs cases. Most patients admitted to the COVID-19 ICU had severe COVID-19 infection manifested as bilateral pneumonia. Interestingly, there was no significant difference in APACHE II and SOFA scores between MDRGN bacteria BSIs cases with negative and positive outcome. However, SAPS II score was significantly higher in patients with short-term negative outcome. Our study once again confirmed that SAPS II score is a powerful tool for risk stratification of patients with negative outcome[8]. The dominant MDRGN bacteria in our COVID-19 unit was Acinetobacter baumannii, what is the opposite of the present studies[1]. The explanation is that local epidemiological parameters, pathogens and they resistance mechanism different from different regions. Also, designed study parameters and their definition could also vary from different studies. Due to these reasons microbiological studies are difficult to compare. In our study we investigated inflammatory parameters at two time points: the day of the COVID-19 ICU admission and the day when MDRGN bacteria BSIs was confirmed by positive blood culture. The goal was to demonstrate if the early measured inflammatory parameters and their dynamic change in COVID-19 critically ill patients with exaggerated sys-

temic inflammatory response could help us difference the bacterial and viral disease and recognize patients prone to MDRGN secondary bacterial infection and start with the appropriate antimicrobial therapy on time. As we already know systemic inflammatory syndrome in severe COVID-19 infection is insensitive indicator of bacterial superinfection and also many non-infectious parameters affect it. However our study did not reveal the significant difference in inflammatory parameters on the day of admission to the COVID-19 ICU between control COVID-19 cases without secondary bacterial infection and COVID-19 cases who developed MDRGN bacteria BSIs during their stay in the COVID19 ICU, except in the PCT values. Those COVID-19 critically ill patients with the critical PCT value of 0,99 mcg/L on the day of admission to the ICU had greater odds for MDRGN bacterial secondary infection. Similar result that PCT values of 1 mcg/L can indicate secondary bacterial infection in COVID-19 patients was confirmed in study[9]. Also our study revealed that MDRGN bacteria BSIs cases had significantly higher leukocytes, neutrophils, NLR and PCT values, but lower lymphocytes and thrombocytes on the day of MDRGN bacteria BSIs confirmation with positive blood culture in comparison to the values on the day of the admission to the COVID-19 ICU. However, we confirmed similar as in another studies that PCT values of 2,46 mcg/L and NLR of 28,9 during intensive care treatment are reliable indicators for high risk of MDRGN bacterial infection origin and time to start with antimicrobial therapy if MDRGN bacteria are dominant microbial pathogens in the ICU[10,11] (table 2,3). To conclude, inflammatory parameters and their dynamics during the COVID-19 ICU stay could help every clinician to improve therapeutic decision on time especially in the hard era of pandemics and hopefully in a timely manner direct the course of critically ill patients on the positive outcome. Also, PCT values have been shown to be a good parameter for risk stratification and careful monitoring of critically ill COVID 19 patients with high chance for MDRGN bacteria BSIs development.

Conclusion

Bloodstream infections caused by MDRGN bacteria are associated with high ICU mortality, as we have seen in the COVID-19 pandemia. Unfortunately, patients with severe COVID-19 infection are prone to MDRGN bacteria BSIs more than non COVID-19 patients. They also represent a great challenge in the treatment for the clinicians. Although, inflammatory parameters measured in our study did not show significant value for the prediction of MDRGN bacteria BSIs on the day of admission to the ICU, PCT values were the only reliable marker for stratification of the critically ill COVID-19 patients with the risk of MDRGN bacteria BSIs growth. Likewise our study showed that monitoring dynamic shift of inflammatory parameters during the ICU stay could reliably help clinician to recognize the MDRGN bacteria BSIs and start with the antimicrobial therapy in a timely manner.

Abbreviations

Bloodstream infections – BSIs; C-reactive protein – CRP; intensive care unit – ICU; multidrug resistant Gram-negative bacteria – MDRGN bacteria; neutrophil/lymphocyte ratio (NLR); procalcitonin – PCT

Conflict of interest:

The authors declare they have no competing interest.

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